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<table border="1"> <caption>Data from Bar Chart: Concentration of IL-8 vs. Concentration of Test Compound</caption> <thead> <tr> <th>Concentration of Test Compound (mM)</th> <th>Concentration of IL-8 (pg/ml)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>~4800</td> </tr> <tr> <td>0.1</td> <td>~4000</td> </tr> <tr> <td>0.5</td> <td>~3200 (***)</td> </tr> <tr> <td>1</td> <td>~2500 (***)</td> </tr> </tbody> </table>				Concentration of Test Compound (mM)	Concentration of IL-8 (pg/ml)	0	~4800	0.1	~4000	0.5	~3200 (***)	1	~2500 (***)
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(57) Abstract													
<p>The present invention provides agents for inhibiting production of interleukin-8 and for inhibiting granulocytes activation as well as novel method for curing inflammatory diseases. The agents for inhibiting production of interleukin-8, and for inhibiting granulocytes activation and for curing inflammatory diseases, which contain as an active ingredient, a carbostyryl derivative represented by general formula (I) (wherein R is a halogen atom; the substitution site of a side-chain of formula (A) is 3- or 4-position in the carbostyryl skeleton; and the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single bond or a double bond) or pharmaceutically acceptable salt thereof.</p>													

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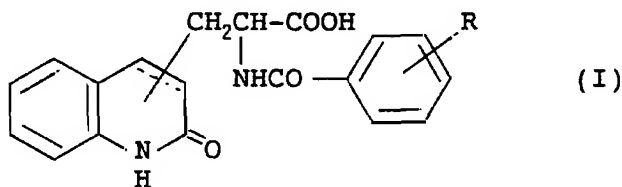
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CARBOSTYRIL DERIVATIVE FOR INHIBITING PRODUCTION OF INTERLEUKIN-8

FIELD OF THE INDUSTRIAL UTILIZATION

The present invention relates to an agent for inhibiting production of interleukin-8, an agent for inhibiting activation of granulocytes, an agent for curing inflammatory diseases, an agent for curing Behçet disease, an agent for curing stomatitis, an agent for curing nephritis and an agent for curing voice disorders. More particularly, the present invention relates to an agent for inhibiting production of interleukin-8, an agent for inhibiting activation of granulocytes, an agent for curing inflammatory diseases, an agent for curing Behçet disease, an agent for curing stomatitis, an agent for curing nephritis and an agent for curing voice disorders, all comprising, as an effective ingredient, a carbostyryl derivative represented by the following general formula (I)



[wherein R is a halogen atom (a fluorine atom, a chlorine atom, a bromine atom or an iodine atom); the substitution site of the substituent on the carbostyryl

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skeleton is 3- or 4-position of the carbostyryl skeleton; and the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single bond or a double bond] or a salt thereof, preferably 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or
5 a salt thereof.

BACKGROUND ART

The carbostyryl derivatives represented by the above general formula (I) and the processes for
10 producting thereof are described in Japanese Patent Publication No. 35623/1988. Further, the usefulness of the carbostyryl derivative as an anti-gastric ulcer agent is described in Japanese Patent Application Kokai (Laid-Open) No. 74329/1991.

15 Also the usefulness of these carbostyryl derivatives as an agent for curing diabetes is described in International Publication No. WO 92/21342; their usefulness as an agent for protecting intestinal mucosa from disorders is described in International Publication
20 No. WO 94/12182; and their usefulness as an agent for inhibiting reduction in somatostatin secretion is described in International Publication No. WO 93/24043.

Interleukin-8 (hereinafter abbreviated to IL-8), which is also called a neutrophil leucocytes-
25 activating factor, is a basic heparin binding polypeptide composed of 72 amino acids and is a cytokine produced not only from activated macrophages but also

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from various types of human cells.

IL-8 has various physiological activities such as the followings. (1) IL-8 is a chemotactic factor to neutrophil leucocytes, T cells and basophil leucocytes; (2) IL-8 activates neutrophil leucocytes, releases a lysosomal enzyme, changes the adhesion of neutrophil leucocytes to the endothelial cells of blood cells, and exasperates the inhibitory effect for propagation of candida species; (3) IL-8, when injected into joints, gives rise to destruction of synovial membrane accompanied with wetting of a large amount of neutrophil leucocytes; (4) IL-8 increases the appearance of adhesion factor on the surface of neutrophil leucocytes; (5) IL-8 controls the release of histamine from basophil leucocytes; and (6) IL-8 activates neutrophil leucocytes in artificial organs. IL-8 is also called as an inflammatory cytokine, and abnormal production of IL-8 and excessive reaction to IL-8 are thought to cause inflammatory diseases.

Behçet disease is a peculiar systemic inflammatory disease which attacks the mucous membrane of oral cavity, eyes, pudenda, skin and nearly all organs. The cause of the disease is said to be connected with infection, immunological abnormality, etc. but is not clarified yet. In curing the disease, there are used steroidal hormones, colchicine, Endoxan, cyclosporins, etc., but they must be used with the greatest possible care in view of their side effects.

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No useful curing agent has been found yet which is safe and can be administered over a long period.

The aphthous stomatitis caused by diseases such as stomatitis and the like is difficult to clinically distinguish from the aphthous stomatitis caused by Behçet disease and, similarly to Behçet disease, is intractable and recur often. In curing the disease, nosotropic therapies such as local administration of steroidal hormones, coating of silver nitrate, and the like are applied because the cause of stomatitis is unclear in many cases. In these therapies, however, continuous application is difficult because of, for example, the side effect of the substance used and, when the therapy is stopped, there is often seen recurrence of the disease. No useful curing agent has been found yet which is safe and can be administered over a long period. Stomatitis often shows an ulcerative symptom but there is no report mentioning that any anti-gastric ulcer agent is useful for such stomatitis.

Nephritis is thought to be caused not only by infection and an immunological mechanism but also by a nonimmunological mechanism. When nephritis is caused, for example, by various other diseases such as serum coagulation system disease, fibrinolytic system disease, hypertension and the like, it is said that nephritis is also induced by the quality of meal, etc. Thus, nephritis is a very complicated disease and is very difficult to cure. Hence, many researches are under way

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in order to find out an effective method for curing nephritis.

Curing of nephritis has hitherto been conducted by administering various drugs such as
5 steroidal drug, immunosuppressive agent, non-steroidal anti-inflammatory agent, anticoagulant, antithrombocyte agent and the like. However, the steroidal drug shows a side effect when administered in a large amount over a long period; the immunosuppressive agent, showing a more
10 striking side effect, must be used and applied with sufficient care; and the anticoagulant and the anti-thrombocyte agent are merely for alleviating the condition of nephritis and do not cure the root cause of the disease.

15 Hence, it is desired that the mechanism of nephritis development is clarified fully, that a reasonable method for curing nephritis is established and that a drug is developed which is effective for nephritis and which can be used safely over a long
20 period.

In recent years, there has often been seen a case in which the excessive utterance required in special occupations owing to the change in social needs causes chorditis and consequent voice disorders. In
25 such a case, since the excessive utterance is forced for occupational reasons, the voice disorders cannot be cured by silence cure, etc. when the patient is unable to be freed from work. As a result, the vocal cord

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having inflammation is used excessively and it is often difficult to improve the voice disorders by an ordinary conservative cure alone. Hence, various researches are under way on a drug suitably used for cure of voice disorders. The methods currently used for curing voice disorders include spraying the throat with a vasoconstrictor or an adrenocortical hormone (this is an supplementary method), but the spraying method has a safety problem when continuously used over a long period. It is therefore desired to develop a drug which is low in side effect and which can be used safely over a long period.

DISCLOSURE OF THE INVENTION

The present inventors made extensive study in order to find a drug which is useful for the cure of inflammatory diseases because of its activity for cytokine as well as for activation and adhesivity of granulocytes and which can be used safely over a long period for the cure of Behçet disease, stomatitis, nephritis and voice disorders. As a result, the present inventors found out that the carbostyryl derivatives represented by the above-mentioned general formula (I) or their salts, particularly 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or its salt has an excellent inhibitory activity for IL-8 production from IL-8 producing cells, an inhibitory activity for activation of granulocytes and an inhibitory activity

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for expression of adhesion factor of granulocytes; is effective for Behçet disease; is effective for the cure of painful- or painless-aphthous stomatitis which is caused by diseases such as stomatitis and the like and
5 which gives the same symptom as Behçet disease; and is effective as an agent for curing diseases caused by increasing of the IL-8 production, an agent for curing diseases caused by the activation of granulocytes, an agent for curing diseases caused by increasing of the
10 expression of adhesion factor of granulocytes, an agent for curing nephritis and an agent for curing voice disorders.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the inhibitory
15 activity of the present compound used as a test compound, i.e. 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid for the acceleration of IL-8 production from IL-8 producing cells by Helicobacter pylori (hereinafter referred to as H. pylori).

20 Fig. 2 is a graph showing the inhibitory activity of the present compound used as a test compound, i.e. 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid for the activation of neutrophil leucocytes by H. pylori.

25 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The agent for inhibiting interleukin-8

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production, agent for inhibiting activation of granulocytes, agent for curing inflammatory diseases, agent for curing Behçet disease, agent for curing stomatitis, agent for curing nephritis and agent for curing voice disorders all according to the present invention, are obtained by converting a carbostyryl derivative represented by general formula (I) or its salt into an ordinary pharmaceutical preparation.

Such a pharmaceutical preparation is prepared by using diluting agents or excipients ordinarily used, such as filler, bulking agent, binder, wetting agent, disintegrator, surfactant, lubricant and the like. The pharmaceutical preparation can be prepared in various forms depending upon the purpose of curing intended. Typical examples of the forms are tablets, pills, a powder, a solution, a suspension, an emulsion, granules, capsules, suppositories, an injection (e.g. solution or suspension) and an external preparation. It is also possible to use the compound of general formula (I) or its salt by mixing it with a resin or the like to increase its sustained releasability.

In preparing tablets, there can be used various carriers known in the art, exemplified by excipients such as lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid and the like; binders such as water, ethanol, propanol, simple syrup, lactose solution, starch solution, gelatin

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solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone and the like; disintegrators such as dry starch, sodium alginate, powdered agar, powdered laminarin, sodium

5 hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan-fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride, starch, lactose and the like; disintegration inhibitors such as white sugar, stearin, cacao butter, hydrogenated oil and the like;

10 absorption promoters such as quaternary ammonium salts, sodium lauryl sulfate and the like; humectants such as glycerine, starch and the like; adsorbents such as starch, lactose, kaolin, bentonite, colloidal silicic acid and the like; and lubricants such as refined talc,

15 stearic acid salts, boric acid powder, polyethylene glycol and the like. The tablets can be prepared, as necessary, in the form of ordinary coated tablets, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets or film-coated tablets, or in the form of

20 double-layered tablets or multi-layered tablets.

In preparing pills, there can be used various carriers known in the art, exemplified by excipients such as glucose, lactose, starch, cacao butter, hardened vegetable oils, kaolin, talc and the like; binders such

25 as powdered acacia, powdered tragacanth, gelatin, ethanol and the like; and disintegrators such as laminarin, agar and the like.

In preparing suppositories, there can be used

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carriers known in the art, exemplified by a polyethylene glycol, cacao butter, a higher alcohol, a higher alcohol ester, gelatin and a semi-synthetic glyceride.

In preparing an injection (solution, emulsion
5 or suspension), it is generally sterilized and is preferably made isotonic to the blood. In preparing the solution, emulsion or suspension, there can be used all diluents commonly used in the art, such as water, ethyl alcohol, propylene glycol, ethoxylated isostearyl alco-
10 hol, polyoxyisostearyl alcohol and polyoxyethylene sorbitan-fatty acid esters. In this case, the injection may contain sodium chloride, glucose or glycerine in an amount sufficient to make the injection isotonic, and may further contain a solubilizing agent, a buffer
15 solution, a soothing agent, etc. all ordinarily used. The injection may furthermore contain, as necessary, a coloring agent, a preservative, a perfume, a flavoring agent, a sweetening agent and other drugs.

The external preparation is prepared in the
20 form of ordinary external preparation for pharmaceutical use. The ordinary external preparation for pharmaceutical use includes, for example, a solution, an oil, a lotion, a liniment, a fatty oil-based ointment, an emulsion type ointment (e.g., O/W type hydrophilic ointment
25 or W/O type water-absorbing ointment), a water-soluble ointment, a paste, a plaster, a cream and an emulsion. The ordinary external preparation for pharmaceutical use is not restricted to the above Examples. Each of these

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forms can be prepared according to an ordinary method.

In shaping the external preparation, there can be used various materials known in the art. As the base, for example, there can be used at least one base
5 selected from various oily bases or various water-soluble bases. Specific examples of the base are oils and fats such as peanut oil, sesame oil, soybean oil, safflower oil, avocado oil, sunflower oil, corn oil, rape seed oil, castor oil, camellia oil, coconut oil,
10 olive oil, poppy seed oil, cacao oil, beef tallow, lard, wool fat and the like; modified oils and fats obtained by subjecting the above-mentioned oils and fats to chemical treatments (e.g. hydrogenation); mineral oils such as petrolatum, paraffin, silicone oil, squalane and
15 the like; higher fatty acid esters, higher aliphatic alcohols and waxes such as isopropyl myristate, N-butyl myristate, isopropyl linoleate, propyl ricinoleate, isopropyl ricinoleate, isobutyl ricinoleate, heptyl ricinoleate, diethyl sebacate, diisopropyl adipate,
20 cetyl alcohol, stearyl alcohol, bleached bees wax, spermaceti, Japan wax, hydrous lanolin, carnauba wax, shellac wax and the like; higher fatty acids such as stearic acid, oleic acid, palmitic acid and the like; mixtures of mono-, di- and tri-glycerides of saturated
25 or unsaturated fatty acids of 12-18 carbon atoms; polyhydric alcohols such as ethylene glycol, polyethylene glycol, propylene glycol, polypropylene glycol, glycerin, Batyl Alcohol, pentaerythritol, sorbitol,

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mannitol and the like; gummy substances such as acacia, gum benzoin, guaiacum, tragacanth gum and the like; natural water-soluble polymers such as gelatin, starch, casein, dextrin, pectin, sodium pectate, sodium
5 alginate, methyl cellulose, ethyl cellulose, carboxy-methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, nitrocellulose, crystalline cellulose and the like; synthetic water-soluble polymers such as polyvinyl alcohol, polyvinyl methyl ether, polyvinylpyrrolidone,
10 sodium polyacrylate, carboxyvinyl polymer, polyethyleneimine and the like; nonionic, anionic or cationic or amphoteric surfactants; ethanol; isopropanol; and water. In the present invention, these bases can be used singly or in admixture of two or more.

15 The external preparation can contain, as necessary, additives of common use such as gelling agent, preservative, antioxidant, buffer, pH-controlling agent, wetting agent, antiseptic agent, coloring agent, aromatic agent, pigment, thickening agent, metal
20 chelating agent and the like.

 The aerosol type agent is prepared generally by preparing a sterilized solution or suspension containing the effective ingredient and then adding a propellant thereto. In preparing the solution or
25 suspension, there can be used all diluents commonly used in the art, such as those mentioned with respect to the injection. As to the propellant, there can be used all propellants commonly used in the art, such as liquefied

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gas propellants for example, chlorofluorocarbons (e.g., Flon 12 or Flon 123), compressed gas propellants (e.g., nitrogen gas and carbon dioxide) and the like. The aerosol type agent may further contain a solubilizing agent, a buffer solution, etc., which are used commonly and, if necessary, the aerosol type agent may contain a coloring agent, a preservative, a perfume, a flavoring agent, a sweetening agent, etc.

The agent for inhibiting production of IL-8 of the present invention is useful for the prevention and cure of acute as well as chronic inflammatory diseases, based on the inhibitory activity for IL-8 production as well as on the inhibitory activity for activation of granulocytes. The agent is also useful for increasing the biocompatibilities of artificial organs and of artificial blood vessels. The inflammatory diseases include, for example, inflammatory dermal diseases such as inflammatory keratosis (e.g. psoriasis), atopic dermatitis, contact dermatitis and the like; chronic inflammatory diseases such as chronic rheumatoid arthritis, systemic lupus erythematosus (SLE), Behçet disease and the like (these are autoimmune diseases); inflammatory intestinal diseases such as Crohn disease, ulcerative colitis and the like; inflammatory hepatic diseases such as hepatitis B, hepatitis C, alcoholic hepatitis, drug allergic hepatitis and the like; inflammatory renal diseases such as glomerulonephritis and the like; inflammatory respiratory system diseases

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such as bronchitis and the like; stomatitis; chondritis; and inflammations appearing during the use of artificial organs and artificial blood vessels. The inflammatory diseases to which the present agent is applicable, are
5 not restricted only to the above mentioned examples.

The agent of the present invention inhibits
(1) the acceleration of IL-8 production from IL-8 producing cells (e.g. peripheral blood monocyte, histiocytic macrophage, large granular lymphocyte, T
10 lymphocyte, neutrophil leucocyte, fibroblast, endothelial cells of blood vessel, epidermal cell, liver cell, astral cell, bronchial epithelial cell and gastric carcinoma established cell line) by H. pylori which is said to have a connection with the appearance and
15 recurrence of gastric mucosa injury, (2) the activation of neutrophil leucocytes and (3) the enhancement of adhesion factor. The present agent is therefore useful also for the prevention of appearance and recurrence of the gastric mucosa disorders caused by H. pylori. Since
20 H. pylori not only induces the activation of neutrophil leucocytes but also accelerates the appearance of ICAM-1 (ligand of LFA-1) in endothelial cells of blood vessel and cells of gastric mucosa, the present agent also has an inhibitory activity for the acceleration of
25 appearance of ICAM-1 by H. pylori.

The agent for curing Behçet disease and the agent for curing stomatitis both according to the present invention are used for the cure of various

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diseases of mucosa in oral cavity, eyes, pudenda, skin, etc., caused by Behçet disease. The agent can also be used for the cure of disorders of mucosa in oral cavity, caused by stomatitis, etc. The stomatitis includes, for
5 example, catarrhal stomatitis, ulcerative stomatitis, aphthous stomatitis, herpetic stomatitis and toxic stomatitis.

The agent for curing nephritis according to the present invention is useful for acute, rapidly
10 progressive or chronic nephritis which is thought to be caused by various reasons, and can be used for the cure of, in particular, chronic glomerulonephritis, etc. The acute nephritis includes, for example, glomerulonephritis or IgA glomerulonephritis after infection with
15 hemolytic streptococcus, etc., chronic proliferative nephritis, crescent forming nephritis, lupus nephritis, necroticizing angitis and purpuric nephritis. The rapidly progressive nephritis includes, for example, crescent forming nephritis (extracapillary proliferative glomerulonephritis). The chronic nephritis
20 includes, for example, mesangial proliferative glomerulonephritis, membranous nephritis, membranous proliferative nephritis, focal glomerulonephritis, sclerotic glomerulonephritis or purpuric angitis, and
25 lupus nephritis.

The agent for curing voice disorders according to the present invention is useful for curing voice disorders which are thought to be caused by various

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reasons, and can be used for the cure of voice disorders of, in particular, people who make voices as a profession, such as singers, announcers and the like.

The amount of the carbostyryl derivative (I)
5 or its salt to be contained in the pharmaceutical preparation of the present invention is not particularly restricted and can be appropriately selected from a wide range, and the amount is generally 1-70% by weight, preferably 5-50% by weight in the pharmaceutical
10 preparation.

The method for administering the pharmaceutical preparation is not particularly restricted. It is decided depending upon the form of preparation, the age, distinction of sex and other conditions of patient, the
15 disease condition of patient, etc. For example, tablets, pills, a solution, a suspension, an emulsion, granules or capsules are administered orally. An injection is intravenously administered singly or in admixture with an ordinary auxiliary solution of
20 glucose, amino acids or the like, or, as necessary, is singly administered intramuscularly, intradermally, subcutaneously or intraperitoneally. Suppositories are administered intrarectally. A solution, a suspension or a syrup type agent is orally administered. An aerosol
25 type agent is administered directly onto the throat.

The dose of the present pharmaceutical preparation is appropriately selected depending upon the administration method, the age, distinction of sex and

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other conditions of patient, the disease condition of patient, etc., and the desirable dose is generally about 0.6-50 mg per kg of body weight per day in terms of the amount of the carbostyryl derivative (1) or its salt.

- 5 The desirable content of the effective ingredient in each unit of administration form is 10-1,000 mg.

EXAMPLES

- The present agent is hereinafter described more specifically by showing Preparation Examples and
- 10 Pharmacological Tests.

Preparation Example 1

- | | | |
|----|---|-------|
| | 2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid | 150 g |
| | Avicel (trade name for microcrystalline cellulose, product of Asahi Chemical Industry Co., Ltd. | 40 g |
| | Corn starch | 30 g |
| 15 | Magnesium stearate | 2 g |
| | Hydroxypropylmethyl cellulose | 10 g |
| | Polyethylene glycol 6000 | 3 g |
| | Castor oil | 40 g |
| | Methanol | 40 g |
- 20 2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid, Avicel, corn starch and magnesium stearate were mixed together and ground, then the mixture was made into tablets by using a tablet machine with a punch (R 10 mm). The tablets were coated with a

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film-coating agent consisting of hydroxypropylmethyl cellulose, polyethylene glycol 6000, castor oil and methanol, to produce film-coated tablets.

Preparation Example 2

5	2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid	150 g
	Citric acid	1.0 g
	Lactose	33.5 g
	Dicalcium phosphate	70.0 g
	Prulonic F-68	30.0 g
10	Sodium lauryl sulfate	15.0 g
	Polyvinylpyrrolidone	15.0 g
	Polyethylene glycol (Carbowax 1500)	4.5 g
	Polyethylene glycol (Carbowax 6000)	45.0 g
	Corn starch	30.0 g
15	Dry sodium lauryl sulfate	3.0 g
	Dry magnesium stearate	3.0 g
	Ethanol	A sufficient quantity

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid, citric acid, lactose, dicalcium phosphate, Prulonic F-68 and sodium lauryl sulfate were mixed together.

The mixture was sieved through a No. 60 screen. The resulting sieved mixture was wet-granulated with an ethanol solution containing polyvinylpyrrolidone, Carbowax 1500 and Carbowax 6000. As necessary, ethanol was added to convert the mixture into

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a paste-like mass. Corn starch was added, and mixing was continued until uniform particles were formed. The resulting material was passed through a No. 10 screen, then placed in a tray, and dried in an oven of 100°C for 5 12-14 hours. The dried particles were sieved through a No. 16 screen. To the resulting material were added dry sodium lauryl sulfate and dry magnesium stearate. The mixture was compressed into core tablets of desired shape with a tablet machine.

10 The core tablets were treated with a varnish and then sprayed with talc for prevention of moisture absorption. On the resulting core tablets was formed an undercoat layer. Sufficient times of varnish coating was conducted for internal use. Formation of undercoat 15 layer and smooth coating were conducted to obtain completely round and smooth tablets. Color coating was conducted until a desired color was obtained. After drying, the coated tablets were polished to obtain tablets of uniform gloss.

20 Preparation Example 3

	2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid	5 g
	Polyethylene glycol (molecular weight: 4000)	0.3 g
	Sodium chloride	0.9 g
	Polyoxyethylene sorbitan monooleate	0.4 g
25	Sodium metabisulfite	0.1 g
	Methylparaben	0.18 g

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Propylparaben	0.02 g
Distilled water for injection	10.0 ml

The parabens, sodium metabisulfite and sodium chloride were dissolved in the above distilled water of half the above volume at 80°C with stirring. The solution was cooled to 40°C, and therein were dissolved 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid, polyethylene glycol and polyoxyethylene sorbitan monooleate. To the solution was added the remaining distilled water to make a final volume. The solution was sterilized by passing through an appropriate filter paper, to prepare an injection.

Pharmacological Test 1

Inhibitory activity for production of IL-8

1) Cells used: Human gastric cancer strain MKN 45 incubated in RPMI 1640 culture medium containing 10% of heat inactivated FCS (fetal calf serum).

2) Stimulating substance for production of IL-8

Clinically isolated H. pylori C0001 (obtained from Department of Internal Medicine, the Ohkura National Hospital).

The bacterium (H. pylori) was incubated in a Brucella broth containing 7% of FCS and was used in an exponential growth phase.

3) Test compound

2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid

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4) Test method

A human gastric cancer cell line MKN 45 was inoculated on a 24-well culture plate in an amount of 0.3×10^6 cells/well. After the cells had adhered to the plate, the culture medium was changed to RPMI culture medium without antibiotic substance containing 10% of FCS. Thereto was added H. pylori (clinical isolate C0001) in an amount of 1.2×10^7 cfu (cells:bacterium = 1:400), after which incubation was conducted at a CO₂ concentration of 5% at 37°C for 24 hours. The resulting mixture was subjected to centrifugation; the supernatant was recovered; and the amount of IL-8 in the supernatant was measured by EIA (enzyme immunoassay) according to a sandwich method [Microbiol. Immunol., vol. 36 (5), pp. 507-516, 1992].

5) Test Results

The test results are shown in Fig. 1. In Fig. 1, each data is shown as average \pm SE, of four-time measurements, and each *** indicates $p < 0.001$. As shown in Fig. 1, the test compound inhibited production of IL-8 from human gastric cancer MKN 45 cells, dependently upon the amount of the test compound used. Incidentally, the test compound showed no cytotoxicity when used in a concentration up to 5 mM.

25 Pharmacological Test 2Effect on the activation of granulocytes

1) Cells used: Human neutrophil leucocytes isolated by

- 22 -

the dextran Ficoll Paque sedimentation method.

2) Activating substance: H. pylori cultured supernatant

H. pylori (standard strain ATCC 43504) was incubated in Brucella broth containing 7% of heat inactivated FCS for 3 days. The resulting culture medium was subjected to centrifugation at 3,500 rpm for 10 minutes. The supernatant was filtered for sterilization.

3) Test compound

10 2-(4-Chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid

This test compound was used by making into a 20 mM solution using NaOH and then diluting the solution with a culture medium for assay.

15 As to the antibody for surface antigen (CD11b), there was used FITC labelled CD11b (manufacture by Becton, Dickinson & Co.).

As to the culture medium for assay, there was used a RPMI culture medium containing 10% of FCS.

20 4) Test method .

Human neutrophil leucocytes were inoculated on a 24-well culture plate in an amount of 5×10^5 cells/well. The wells were divided into a group (A) to which nothing was added (containing only neutrophil leucocytes), a group (B) to which H. pylori cultured supernatant (final concentration = 2%) was added, and a group (C) to which H. pylori cultured supernatant (final concentration = 2%) and the test compound (final concentration = 10 μ M,

- 23 -

50 μ M, 100 μ M or 500 μ M) were added.

Each of 24- well culture plate was incubated in an incubator under an atmosphere containing 10% of CO₂, at 37°C for 2 hours. After the incubation, the neutrophil leucocytes in each well were recovered, washed once with a FCM buffer solution (0.1% bovine serum albumin, 0.1% NaN₃/phosphate-buffered saline), and then were reacted with the FITC labelled CD11b (antibody) on ice for 30 minutes. After the reaction, the reaction mixture was washed with the FCM buffer solution and analyzed by a flow cytometer. From the resulting histogram was calculated an average fluorescent intensity. By taking the appearance of CD11b in the non-stimulated neutrophil leucocytes (containing no H. pylori cultured supernatant) as 100%, there was calculated the relative appearance of CD11b in each group.

5) Test results

The test results are shown in Fig. 2. In Fig. 2, each data is shown as average \pm SE, of four-time measurements; ** indicates $p < 0.01$; and each *** indicates $p < 0.001$. Symbol A is the results of the group (A); B is the result of the group (B); and C¹, C², C³ and C⁴ are the results of the group (C) and are the results when the test compound was added at final concentrations of 10 μ M, 50 μ M, 100 μ M and 500 μ M, respectively. As shown in Fig. 2, the test compound inhibited the H. pylori's activity of augmentation of surface antigen,

- 24 -

dependently upon the amount of the compound used.

Pharmacological Test 3

Test for examining the effect on stomatitis

1) Testees

5 There were tested eight patients of Behçet disease having aphthous ulcer in their oral cavities (age = 18-45 years old, consisting of five males and three females).

2) Method of administration

10 In addition to the cure which had been conducted, 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid was administered three times each day [one tablet each time (one tablet contained 100 mg of said compound)] for 6 months.

15 3) Method for evaluation

Each testee was requested to daily record "number of aphthous ulcers in oral cavity" and "degree of pain". They were each summed up monthly and their changes were calculated as follows.

20 Change in number of aphthous ulcers in oral cavity (%) = $\frac{1 - (a)}{(b)} \times 100$

(a): total number of aphthous ulcers during one month administration

(b): total number of aphthous ulcers during one month before administration

Change in degree of pain (%) = $\frac{1 - (c)}{(d)} \times 100$

(c): total point of degree of pain during one month administration

- 25 -

(d): total point of degree of pain during one month before administration

Incidentally, degree of pain was expressed as a point according to the following six-stage standard.

0: no pain

5 1: pain of no worry

2: not so strong pain

3: worrying pain

4: strong pain

5: very strong pain

10 Based on the changes (%), evaluation was made according to the following seven-stage standard.

Remarkable improvement: 60% or above

Improvement: 30% to below 60%

Slight improvement: 10% to below 30%

15 No change: below 10% to above -10%

Slight aggravation: -10% to above -30%

Aggravation: -30% to above -70%

Distinct aggravation: -70% or below

4) Results

20 With respect to the effect on the number of aphthous ulcers in oral cavity, four patients showed remarkable improvement; one patient showed improvement; two patients showed slight improvement; and one patient showed aggravation. With respect to the effect on pain,

25 five patients showed remarkable improvement; one patient showed slight improvement; and two patients showed aggravation.

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Pharmacological Test 4Test for examining the effect on nephritis

1) Testees

Sixteen (16) persons who were confirmed by
5 diagnosis to have chronic glomerulonephritis (age: 18-66
years old, consisting of ten males and six females).

2) Method of administration

Tablets each containing 100 mg of 2-(4-chloro-
benzoylamino)-3-(2-quinolon-4-yl)propionic acid was
10 orally administered three times each day (one tablet
each time) for 12 weeks.

3) Method of evaluation

The urines which each testee discharged for 2-
3 days before administration and for 2-3 days after
15 administration of 12 weeks, were each accumulated. Each
accumulated urine was measured for amount of urinary
proteins. From each urinary protein amount obtained
thus, its average amount per day was calculated. A
decreasing value (%) in urinary protein amount was
20 calculated from the following formula.

$$\text{Decreasing value in urinary proteins (\%)} = \frac{1 - (e)}{(f)} \times 100$$

(e): daily average of urinary protein amount after
administration;

(f): daily average of urinary protein amount before
administration.

Based on the decreasing value in urinary
25 protein (%), evaluation was made according to the
following four-stage standard.

- 27 -

Improvement: 50% or above

Slight improvement: 25% or above to below 50%

No change: -25% or above to below 25%

Aggravation: below -25%

5 4) Test Results

Six persons showed improvement; two persons showed slight improvement; seven persons showed no change; and one person showed aggravation. Thus, half of the testees showed improvement or slight improvement.

10 Pharmacological Test 5

Test for examining the effect on voice disorders

1) Testees

Ten persons (singers, teachers, instructors of Chinese poem recitation, students of vocal music course in music academy, etc.) who were confirmed by diagnosis to have chondritis and consequent voice disorders as a result of excessive use of vocal cord for vocalization. Their ages ranged from 19 to 65 years old and they consisted of two males and eight females.

20 2) Method of administration

Tablets each containing 100 mg of 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid was administered three times each day (one tablet each time). The administration was made continuously for 2-4 weeks until inflammation (when judged objectively) and voice disorders (when judged subjectively and objectively) came to show improvement.

- 28 -

3) Method of evaluation

The method for measuring the degree of voice disorders objectively by acoustic analysis, etc. is not established yet. Meanwhile, people who make voice for profession, are said to have rubefaction in the mucosa of vocal cord even in their normal conditions. In view of these matters, the effect of cure for voice disorders was evaluated based mainly on the degree of improvement in husky voice (judged subjectively) and the auditory examination made objectively, by referring to the objective observation of inflammation (e.g. rubefaction or swelling in mucosa of vocal cord) using an indirect larynx mirror, a stroboscope or the like.

The degree of husky voice was classified into the following four stages.

3: very strong

2: strong

1: slight

0: None

Using the above classification, the effect of cure for voice disorders was evaluated according to the following standard.

Remarkable effect: the degree of husky voice improved by three stages in four weeks.

Effect: the degree of husky voice improved by two stages in four weeks.

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Slight effect: the degree of husky voice improved
by one stage in four weeks.

No effect: No improvement in degree of husky voice

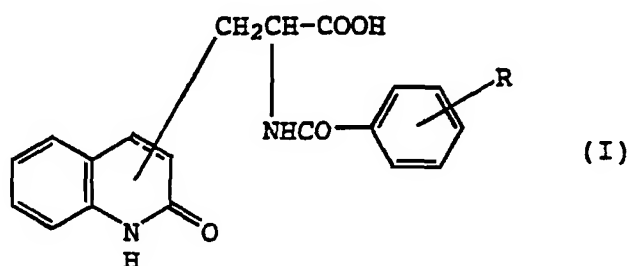
4) Results

- 5 Of the ten testees, three showed effect; three showed slight effect; and there was no testee who showed no effect. Further, there was no side effect which was considered to be due to the test compound used.

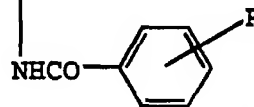
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CLAIMS

1. An agent for inhibiting production of interleukin-8, inhibiting expression of adhesion of granulocytes or inhibiting granulocytes activation which contains, as an active ingredient a carbostyryl derivative represented by the general formula (I):



(wherein R is a halogen atom; the substitution site of side-chain of the formula: $-\text{CH}_2\text{CH}(\text{COOH})$



is 3- or 4-position in the carbostyryl skeleton; and the carbon-carbon bond between 3- and 4-positions in the carbostyryl skeleton is a single bond or a double bond), or salt thereof.

2. The agent according to Claim 1, wherein the carbostyryl derivative represented by the general formula (I), or salt thereof is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or pharmaceutically acceptable salt thereof.

1 3. An agent for preventing or curing inflammatory
dermal disease, autoimmune disease, inflammatory renal
disease inflammatory respiratory disease, stomatitis
or chondritis which contains, as an active ingredient,
5 a carbostyryl derivative represented by the general
formula (I) or salt thereof as claimed in Claim 1.

4. The agent according to Claim 3, wherein
the carbostyryl derivative represented by the general
formula (I), or salt thereof is 2-(4-chlorobenzoyl-
10 amino)-3-(2-quinolon-4-yl)propionic acid or pharma-
ceutically acceptable salt thereof.

5. An agent for preventing or curing injury of
gastric mucosa caused by the infection with Helicobacter
pyroli which contains, as an active ingredient, a
15 carbostyryl derivative represented by the general
formula (I) or salt thereof as claimed in Claim 1.

6. The agent according to Claim 5, wherein
the carbostyryl derivative represented by the general
formula (I) or salt thereof is 2-(4-chlorobenzoylamino)-
20 3-(2-quinolon-4-yl)propionic acid or pharmaceutically
acceptable salt thereof.

7. An agent for improving the bio-acceptability
of an artificial organ or artificial blood vessel which
contains, as an active ingredient, a carbostyryl deriva-
25 tive represented by the general formula (I) or salt
thereof as claimed in Claim 1.

8. The agent according to Claim 7, wherein the

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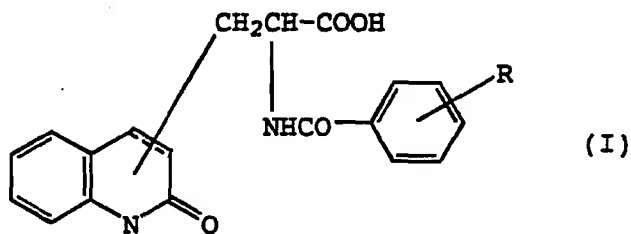
- 1 carbostyryl derivative represented by the general formula
(I) or salt thereof is 2-(4-chlorobenzoylamino)-3-(2-
quinolon-4-yl)propionic acid or pharmaceutically
acceptable salt thereof.
- 5 9. An agent for curing Behçet disease, which
contains, as an active ingredient, a carbostyryl
derivative represented by the general formula (I) or
salt thereof as claimed in Claim 1.
- 10 10. The agent according to Claim 9, wherein
the carbostyryl derivative represented by the general
formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
thereof.
- 15 11. An agent for curing stomatitis, which contains
as an active ingredient, a carbostyryl derivative
represented by the general formula (I) or salt thereof
as claimed in Claim 1.
- 20 12. The agent according to Claim 11, wherein
the carbostyryl derivative represented by the general
formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
thereof.
- 25 13. An agent for curing renal disease, which
contains as an active ingredient, a carbostyryl deriva-
tive represented by the general formula (I) or salt
thereof as claimed in Claim 1.
14. The agent according to Claim 13, wherein

1 the carbostyryl derivative represented by the general
formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
thereof.

5 15. An agent for curing voice disorder, which
contains as an active ingredient, a carbostyryl deriva-
tive represented by the general formula (I) or salt
thereof as claimed in Claim 1.

16. The agent according to Claim 15, wherein
10 the carbostyryl derivative represented by the general
formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
thereof.

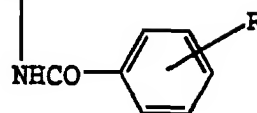
17. Method for inhibiting production of
15 interleukin-8, inhibiting expression of adhesion of
granulocytes or inhibiting granulocytes activation,
by administering a carbostyryl derivative represented
by the general formula (I):



(wherein R is a halogen atom; the substitution site of

- 34 -

1 side-chain of the formula: $-\text{CH}_2\text{CH}-\text{COOH}$



is 3- or 4-position in the carbostyryl skeleton; and
the carbon-carbon bond between 3- and 4-positions in the
carbostyryl skeleton is a single bond or a double bond),
5 or salt thereof.

18. The method according to Claim 17, wherein
the carbostyryl derivative represented by the general
formula (I), or salt thereof is 2-(4-chlorobenzoyl-
amino)-3-(2-quinolon-4-yl)propionic acid or pharma-
10 ceutically acceptable salt thereof.

19. Method for preventing or curing inflammatory
dermal disease, autoimmune disease, inflammatory renal
disease, inflammatory respiratory disease, somatitis and
chorditis, by administering a carbostyryl derivative
15 represented by the general formula (I) as claimed in
Claim 17 or salt thereof.

20. The method according to Claim 19, wherein
the carbostyryl derivative represented by the general
formula (I) or salt thereof is 2-(4-chlorobenzoylamino)-
20 3-(2-quinolon-4-yl)propionic acid or pharmaceutically
acceptable salt thereof.

21. Method for preventing or curing injury
of gastoric mucosa caused by the infection with
Helicobacter pylori, by administering a carbostyryl

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1 derivative represented by the general formula (I) or
salt thereof as claimed in Claim 17.

22. The method according to Claim 21, wherein
the carbostyryl derivative represented by the general
5 formula (I) or salt thereof is 2-(4-chlorobenzoylamino)-
3-(2-quinolon-4- yl)propionic acid or pharmaceutically
acceptable salt thereof.

23. Method for improving the bio-acceptability
of an artificial organ or artificial blood vessel, by
10 administering a carbostyryl derivative represented by
the general formula (I) or salt thereof as claimed in
Claim 17.

24. The method according to Claim 23, wherein
the carbostyryl derivative represented by the general
15 formula (I) or salt thereof is 2-(4-chlorobenzoylamino)-
3-(2-quinolon-4- yl)propionic acid or pharmaceutically
acceptable salt thereof.

25. The method according to Claim 19, wherein the
inflammatory dermal disease is an inflammatory keratosis
20 (psoriasis).

26. The method according to Claim 25, wherein
the carbostyryl derivative represented by the general
formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
25 thereof.

27. The method according to Claim 19, wherein the
inflammatory dermal disease is an atopic dermatitis.

1 28. The method according to Claim 27, wherein
the carbostyryl derivative represented by the general
formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
5 thereof.

29. The method according to Claim 19, wherein the
inflammatory dermal disease is a contact dermatitis.

30. The method according to Claim 29, wherein
the carbostyryl derivative represented by the general
10 formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
thereof.

31. The method according to Claim 19, wherein the
autoimmune disease is a chronic rheumatoid arthritis.

15 32. The method according to Claim 31, wherein
the carbostyryl derivative represented by the general
formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
thereof.

20 33. The method according to Claim 19, wherein the
autoimmune disease is a systemic lupus erythmatosus
(SLE).

34. The method according to Claim 33, wherein
the carbostyryl derivative represented by the general
25 formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
thereof.

1 35. The method according to Claim 19, wherein the autoimmune disease is a Behçet disease.

36. The method according to Claim 35, wherein the carbostyryl derivative represented by the general
5 formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or pharmaceutically acceptable salt thereof.

37. The method according to Claim 19, wherein the inflammatory renal disease is a glomerulonephritis.

10 38. The method according to Claim 37, wherein the carbostyryl derivative represented by the general formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-4-yl)propionic acid or pharmaceutically acceptable salt thereof.

15 39. The method according to Claim 19, wherein the inflammatory respiratory system disease is a bronchitis.

40. The method according to Claim 39, wherein the carbostyryl derivative represented by the general formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
20 4-yl)propionic acid or pharmaceutically acceptable salt thereof.

41. Method for curing Behçet disease, by administering a carbostyryl derivative represented by the general formula (I) or salt thereof as claimed in
25 Claim 1.

42. The method according to Claim 41, wherein the carbostyryl derivative represented by the general

1 formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
thereof.

43. Method for curing stomatitis, by administering
5 a carbostyryl derivative represented by the general
formula (I) or salt thereof as claimed in Claim 1.

44. The method according to Claim 43, wherein
the carbostyryl derivative represented by the general
formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
10 4-yl)propionic acid or pharmaceutically acceptable salt
thereof.

45. Method for curing nephritis, by administering
a carbostyryl derivative represented by the general
formula (I) or salt thereof as claimed in Claim 1.

15 46. The method according to Claim 45, wherein
the carbostyryl derivative represented by the general
formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable salt
thereof.

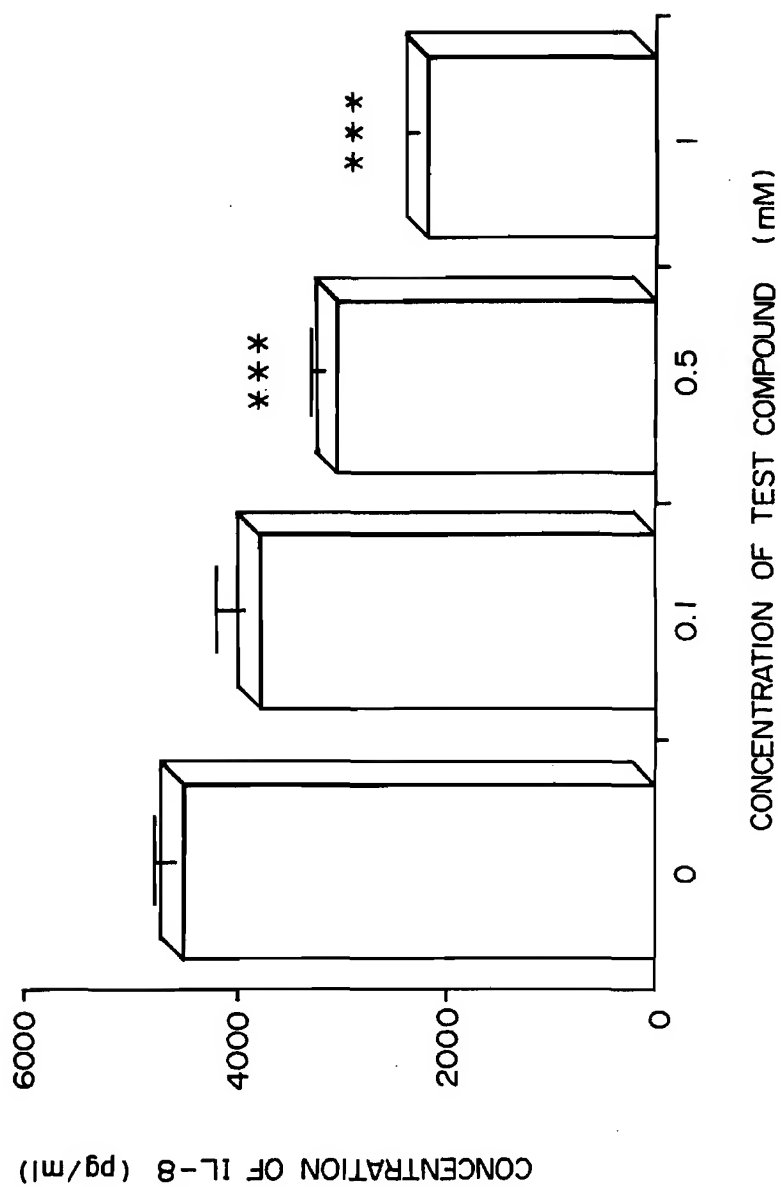
20 47. Method for curing voice disorder, by
administering a carbostyryl derivative represented by
the general formula (I) or salt thereof as claimed in
Claim 1.

48. The method according to Claim 47, wherein
25 the carbostyryl derivative represented by the general
formula (I) is 2-(4-chlorobenzoylamino)-3-(2-quinolon-
4-yl)propionic acid or pharmaceutically acceptable

1 salt thereof.

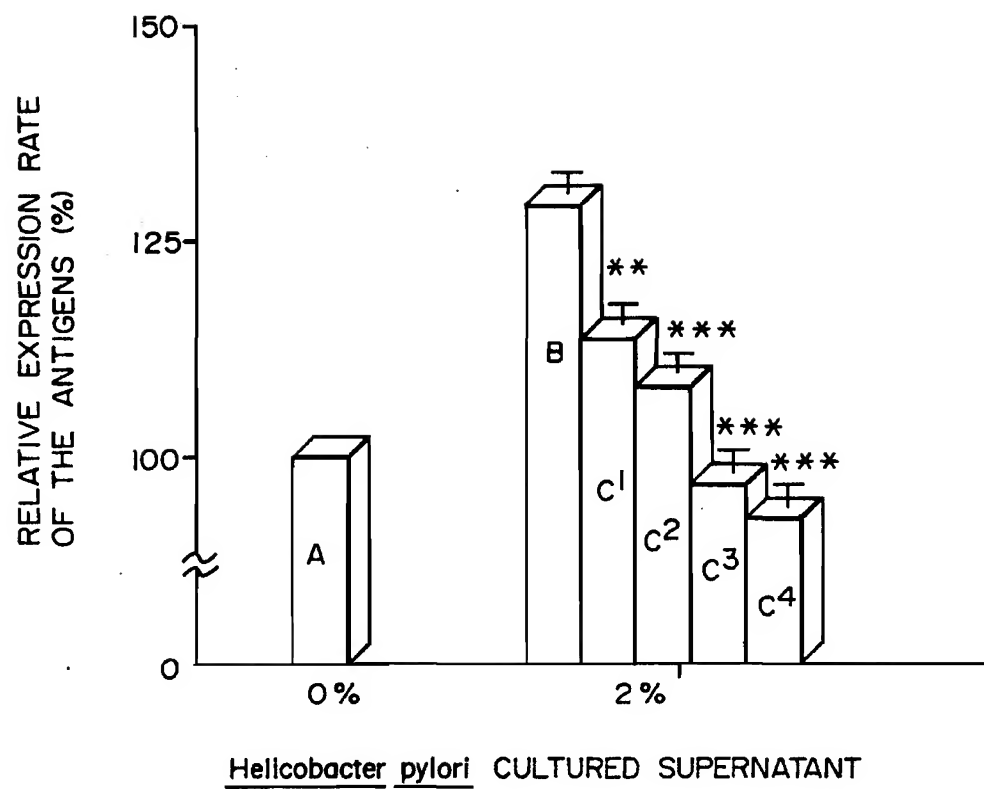
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FIG. 1



2/2

FIG. 2



INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/JP 94/01739

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARZNEIMITTELFORSCHUNG, vol.43, no.3, March 1993 pages 363 - 366 T. YOSHIKAWA ET AL. 'Free radical scavenging activity of the novel anti-ulcer agent Rebamipide studied by electron spin resonance'	1-18,21, 22
Y	see the whole document ---	17-48
X	WO,A,92 21342 (OTSUKA PHARM. CO., LTD.) 10 December 1992 cited in the application	1-16,19, 20
Y	see abstract ---	17-48
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

1 February 1995

Date of mailing of the international search report

10.02.95

Name and mailing address of the ISA

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Fax (+31-70) 340-3016

Authorized officer

Stierman, B

INTERNATIONAL SEARCH REPORT

Inter. Application No

PCT/JP 94/01739

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	NIPPON RINSHO (JAPAN), DEC 1993, VOL. 51, NO. 12, PAGE(S) 3154-8, SUZUKI M ET AL '[Role of ammonia-monochloramine system in Helicobacter pylori--induced gastric mucosal injury]'	1-18,21, 22
Y	see abstract ---	17-48
P,X	WO,A,94 12182 (OTSUKA PHARM. CO., LTD.) 9 June 1994 cited in the application	1-16,21, 22
Y	see page 2 see claims 2,7 ---	17-48
X	RES COMMUN CHEM PATHOL PHARMACOL (UNITED STATES), DEC 1992, VOL. 78, NO. 3, PAGE(S) 259-77, KISHIMOTO S ET AL 'Therapeutic effects of oral rebamipide and in combination with cimetidine on experimental gastritis in rats.'	1-16
Y	see the whole document ---	17-48
X	DE,A,33 24 034 (OTSUKA PHARM. CO. LTD.) 5 January 1984	1-16
Y	see page 24 - page 25 see claim 40 ---	17-48
X	PATENT ABSTRACTS OF JAPAN vol. 15, no. 238 (C-841) (4766) 19 June 1991 & JP,A,03 074 329 (OTSUKA PHARM. CO. LTD.) 28 March 1991	1-16
Y	see abstract ---	17-48
Y	WO,A,93 00902 (OTSUKA PHARM. CO. LTD.) 21 January 1993 see abstract ---	19,20, 31-36
Y	EP,A,0 147 719 (TANABE SEIYAKU CO., LTD.) 10 July 1985 see the whole document ---	17-20, 39,40
Y	DATABASE WPI Week 8826, Derwent Publications Ltd., London, GB; AN 88-180572 & JP,A,63 119 467 (OTSUKA PHARM. CO. LTD.) 24 May 1988 see abstract ---	17-20, 27-30

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INTERNATIONAL SEARCH REPORT

Inter. Application No

PCT/JP 94/01739

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 14, no. 453 (C-764) (4396) 28 September 1990 & JP,A,02 178 227 (OTSUKA PHARM. CO. LTD.) 11 July 1990 see abstract ---	19,20, 37,38, 45,46
P,Y	WO,A,94 20107 (OTSUKA PHARM. CO. LTD.) 15 September 1994 see abstract ---	19,20, 23,24, 31,32, 37,38, 45,46
P,Y	WO,A,94 14444 (OTSUKA PHARM. CO. LTD.) 7 July 1994 see the whole document -----	19,20, 25,26

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 94/01739

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 17-48 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims searched completely: 6,8,10,12,14,22,24,26,28,30,32,34,36,38,40,42,44
Claims searched incompletely: 1-5,7,9,11,13,15-21,23,25,27,29,31,33,35,37,39,41,43,45,47,48;
For further information please see annex.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Continuation of BOX I.2:

As all the different theoretically possible compounds falling under formula I are only exemplified by one example, the search has for economic reasons been restricted to the compound explicitly mentioned in the claims and to the general inventive idea.

The activities mentioned in claim 1 and expressions like "autoimmune disease", "inflammatory dermal disease" ect., do not make sufficiently clear which exact diseases are meant. The search has therefor been restricted to the diseases explicitly mentioned in the claims and to the general inventive concept.

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